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REVIEW ARTICLE OPEN

Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma?

David Price^{1,2}, Leonard Fromer³, Alan Kaplan⁴, Thys van der Molen⁵ and Miguel Román-Rodríguez⁶

Despite current guidelines and the range of available treatments, over a half of patients with asthma continue to suffer from poor symptomatic control and remain at risk of future worsening. Although a number of non-pharmacological measures are crucial for good clinical management of asthma, new therapeutic controller medications will have a role in the future management of the disease. Several long-acting anticholinergic bronchodilators are under investigation or are available for the treatment of respiratory diseases, including tiotropium bromide, aclidinium bromide, glycopyrronium bromide, glycopyrrolate and umeclidinium bromide, although none is yet licensed for the treatment of asthma. A recent Phase III investigation demonstrated that the once-daily long-acting anticholinergic bronchodilator tiotropium bromide improves lung function and reduces the risk of exacerbation in patients with symptomatic asthma, despite the use of inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs). This has prompted the question of what the rationale is for long-acting anticholinergic bronchodilators in asthma. Bronchial smooth muscle contraction is the primary cause of reversible airway narrowing in asthma, and the baseline level of contraction is predominantly set by the level of 'cholinergic tone'. Patients with asthma have increased bronchial smooth muscle tone and mucus hypersecretion, possibly as a result of elevated cholinergic activity, which anticholinergic compounds are known to reduce. Further, anticholinergic compounds may also have anti-inflammatory properties. Thus, evidence suggests that long-acting anticholinergic bronchodilators might offer benefits for the maintenance of asthma control, such as in patients failing to gain control on ICS and a LABA, or those with frequent exacerbations.

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INTRODUCTION

Asthma affects over 300 million individuals worldwide, a figure that is estimated to grow by 100 million by 2025.¹ A chronic inflammatory disease of the airways, asthma has multifactorial pathophysiological causes and considerable heterogeneity in the classification of the disease by phenotype, aetiology, severity and interventional control.

Current guidelines recommend stepwise management to gain and maintain control, in which the clinical definition of full 'control' is daytime symptoms or use of reliever medication less than twice a week, no limitations of activity, no nocturnal symptoms and normal lung function.² Furthermore, the American Thoracic Society and the European Respiratory Society state that any definition or measure of control must take into account the management of a patient's future risk.³ Thus, in clinical management of asthma, consideration must be given to reducing the frequency of exacerbations, preserving lung function, preventing reduced lung growth in children and minimising the adverse effects of any treatment.⁴

For those receiving low-dose inhaled corticosteroids (ICS), current step-up treatment involves the addition of a long-acting β_2 -agonist (LABA) or leukotriene receptor antagonist as controller therapy. In patients unable to attain or maintain control with ICS and LABA—those in Global Initiative for Asthma treatment steps 3–5 (Figure 1)—upward titration of ICS dose, leukotriene modifiers, sustained-release theophylline, oral

glucocorticosteroids and anti-immunoglobulin E (omalizumab) are all further or alternative treatment options.²

Despite these guidelines and the wide range of therapies available, poor control of current asthma symptoms, and of future asthma exacerbations, continues to affect >50% of patients,^{5–9} with exacerbations placing significant strain on their quality of life and on health-care systems.¹⁰ Risk factors associated with future exacerbations include previous exacerbations, poor control, inhaler technique and adherence, co-morbid allergic rhinitis, gastro-oesophageal reflux disease, psychological dysfunction, smoking and obesity.¹⁰ The same factors, in addition to incorrect diagnosis, poor choice of inhaler, variation in individual treatment responses or genetic components, have been attributed to the underlying poor control.¹¹ There are a number of actions available in the primary care setting to reduce the impact of these factors (Figure 1).^{10,11}

In the light of such concerns around risk and poor control, it is appropriate to consider the rationale for investigating additional controller medications. A number of new therapies are under investigation,¹² including long-acting anticholinergic bronchodilators (the focus of this review), anti-prostaglandin D2 CRTH2 antagonists,¹³ phosphodiesterase-4 inhibitors,³ anti-leukotriene 5-lipoxygenase-activating protein antagonists¹⁴ and the monoclonal antibodies mepolizumab and lebrikizumab (which are raised against interleukin-5¹⁵ and interleukin-13,¹⁶ respectively).

Short-acting anticholinergic agents, particularly ipratropium bromide (ipratropium) and oxitropium bromide (oxitropium), have

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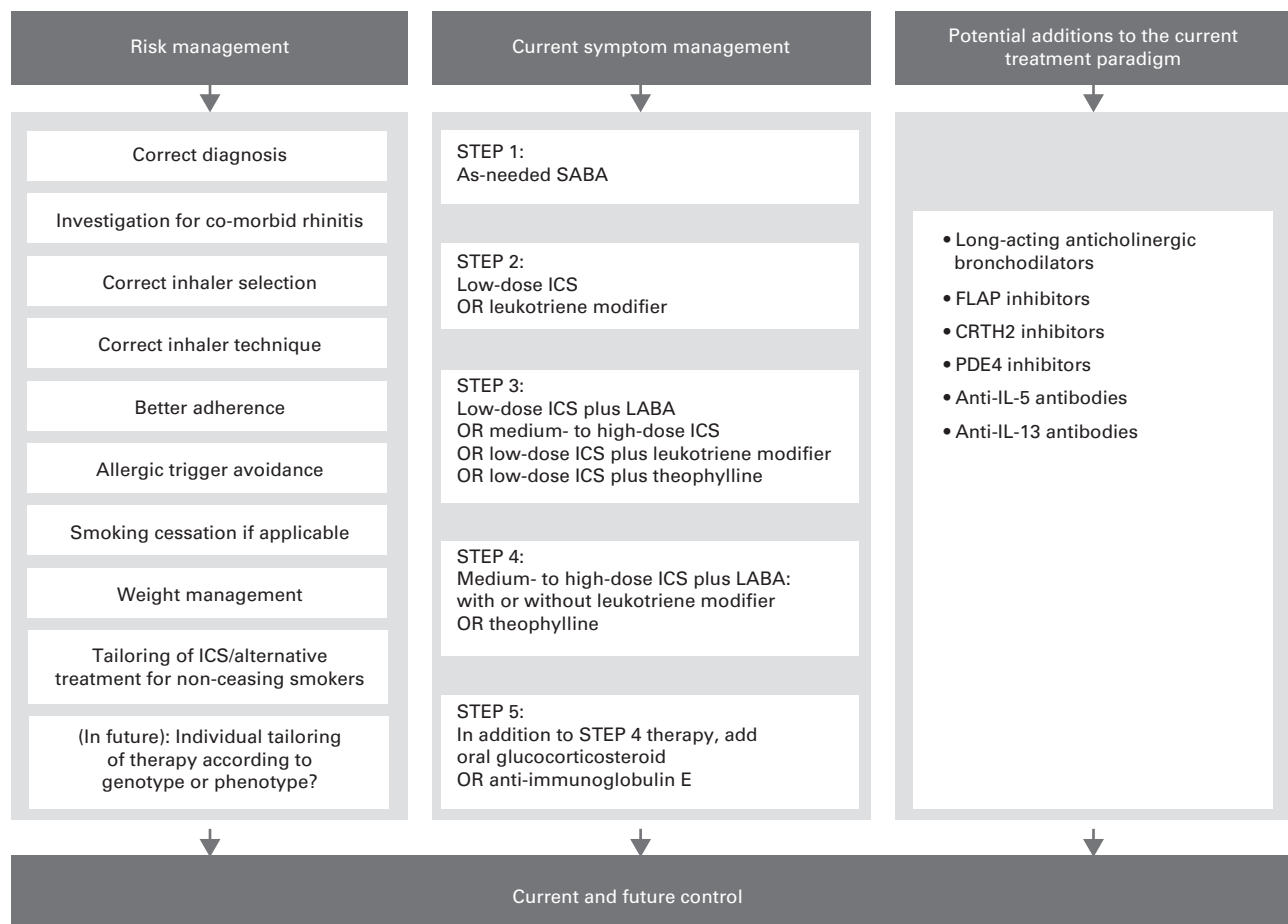


Figure 1. Combined approaches for the management of control in asthma.^{2,5,10–16} FLAP, 5-lipoxygenase-activating protein; ICS, inhaled corticosteroids; IL, interleukin; LABA, long-acting β_2 -agonist; PDE4, phosphodiesterase-4; SABA, short-acting β_2 -agonist.

been used in asthma for many years,^{17,18} although they have not become widespread because they are generally considered to be less effective than short-acting β_2 -agonists (SABAs) for acute bronchodilation.¹⁷ This, coupled with a perception that longer-term antagonism of cholinergic receptors induces little bronchodilation above that induced by LABAs,^{19,20} has meant that, in contrast to chronic obstructive pulmonary disease,^{21,22} long-acting anticholinergic bronchodilators have not been considered or thoroughly investigated as potential controller medication in asthma. Early studies demonstrated mild bronchodilation and protection, over 48 h, against methacholine-induced bronchoconstriction in male patients with asthma,²³ and, in patients with severe persistent asthma, small improvements in lung function were observed with the LABA salmeterol plus the long-acting anticholinergic bronchodilator tiotropium bromide (tiotropium), with a halved dose of fluticasone propionate.²⁴

Recently, Phase I–III clinical investigation with long-acting anticholinergic bronchodilators in asthma has begun: two Phase II trials of umeclidinium bromide (umeclidinium) have completed (NCT01641692; NCT01573624), and Phase II and III trials with tiotropium, as add-on therapy, have demonstrated improvements in lung function and a reduction in exacerbation risk in patients with poorly controlled asthma despite the use of ICS or ICS plus a LABA.^{25–28}

In this review, we consider the pathophysiological and clinical rationales for use of long-acting anticholinergic agents in the broader management of asthma, and the clinical evidence reported to date. Please see Box 1 for a description of the literature search and appraisal methods.

THE ROLE OF CHOLINERGIC ACTIVITY IN THE PATHOPHYSIOLOGY OF ASTHMA

The symptoms of asthma, and of acute exacerbations, are attributed to airway narrowing that occurs as a consequence of chronic inflammation and associated hyper-responsiveness.² Local influx of inflammatory cells and high levels of inflammatory mediators result in airway oedema, airway thickening, mucus hypersecretion and bronchial smooth muscle contraction (Table 1).² Although multiple pathophysiological mechanisms are thought to contribute to the characteristic narrowing of airways and the hyper-responsiveness found in asthma (Table 1),² bronchial smooth muscle contraction represents the primary cause of reversible airway obstruction in asthma.^{29,30} The degree of basal airway smooth muscle contraction (airway smooth muscle 'tone') is under autonomic nervous regulation (Figure 2), although the mechanisms are not fully understood. During normal ventilation, adrenergic sympathetic nerves and parasympathetic cholinergic and non-cholinergic nerves are all active,^{29,31,32} but cholinergic activity is thought to be the predominant driver of bronchoconstriction (Figure 2, Box 2).³¹ Acute treatment with the anticholinergic compounds atropine and ipratropium is known to reduce basal airway smooth muscle tone.^{33,34}

Patients with asthma have increased basal airway smooth muscle tone,³⁵ and there is evidence to suggest that this is a result of increased basal activity of pulmonary parasympathetic cholinergic nerves, hereinafter described as 'cholinergic tone'. Molino *et al.*³⁰ demonstrated that bronchoconstriction induced by breath-holding is significantly inhibited by ipratropium in asthmatic

Box 1 Literature evaluation methods

Clinical evidence around long-acting anticholinergic bronchodilators

We performed searches in November 2013 of PubMed, Google Scholar and Cochrane databases and ClinicalTrials.gov (www.clinicaltrials.gov).

PubMed searches

All terms restricted to title and abstract, with restriction of results to clinical trials:

- (1) Asthma* AND (anticholinergic OR antimuscarinic OR cholinergic OR muscarinic OR parasympathetic)
- (2) Asthma* AND (tiotropium OR umeclidinium OR aclidinium OR glycopyrronium OR darotroprum OR QVA149 OR glycopyrrolate)
- In November 2013 the searches yielded 209 results; search 2 yielded 25 results. PubMed search results were manually reviewed for articles or studies relevant to the topic of short-acting muscarinic agonists or long-acting muscarinic agonists for acute or maintenance therapy

Cochrane database searches

- 'Asthma AND anticholinergic', limited to title, abstract and keywords, yielding 39 hits, the titles and abstracts of which were manually reviewed
- In November 2013 the searches yielded one review¹⁹ relating to the use of anticholinergics for asthma management, and eight reviews of anticholinergics in a variety of acute settings

www.clinicaltrials.gov searches

- Asthma AND tiotropium OR umeclidinium OR aclidinium OR glycopyrronium OR darotroprum OR glycopyrrolate OR QVA149

Pathophysiology and pharmacology

PubMed and Google scholar searches

- The following terms in Boolean strings: asthma; respiratory; cholinergic; muscarinic; parasympathetic; autonomic; tone; pathophysiology; anticholinergic; antimuscarinic; β -agonist; phenotype; genotype; inflammation; bronchoconstriction; and bronchodilation
- As this article is not a systematic review, certain articles within the pathophysiology and pharmacology sections were reviewed and cited based on their adjudged relevance to the topic

Table 1. Mechanisms of airway narrowing and hyper-responsiveness in asthma²

Process	Consequence
Increased volume and/or contractility of airway smooth muscle cells	Excessive contractility of airway smooth muscle
Secretion of multiple bronchoconstriction mediators such as histamine, prostaglandin D ₂ and neurotransmitters	Airway smooth muscle contraction
Uncoupling of airway smooth muscle contraction as a result of inflammatory changes in the airway wall	Excessive narrowing of the airways; loss of maximum plateau of contraction when a bronchodilator is administered
Oedema due to microvascular leakage in response to inflammatory mediators and structural changes to airway smooth muscle	Thickening of airway wall; amplification of airway narrowing due to contraction of airway smooth muscle for geometric reasons
Sensitisation of sensory nerves leading to afferent activity and autonomic reflex	Increased parasympathetic, cholinergic and airway smooth muscle tone, with consequent exaggerated bronchoconstriction in response to sensory stimuli

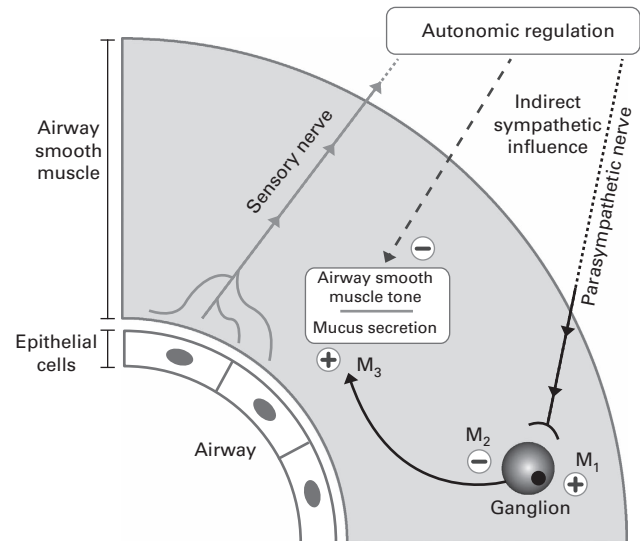


Figure 2. Autonomic regulation of airway smooth muscle tone.^{29,32,49,50} M₁, M₂, M₃, muscarinic acetylcholine receptors 1, 2 and 3. + and – symbols represent signals increasing and decreasing airway smooth muscle tone, respectively. Note that non-adrenergic non-cholinergic autonomic pathways have been omitted for simplicity. Adapted from the study by Cazzola, *et al.*³² with permission from the American Society for Pharmacology and Experimental Therapeutics.

patients but not in healthy volunteers. It is thought that cholinergic tone, at least, is driven by afferent nervous activity arising in the airways,^{29,36,37} and it has been hypothesised that local airway inflammatory mediators may have a role in inducing afferent activity and an autonomic reflex response, thereby driving an increase in cholinergic tone (Figure 2).^{31,38,39} Other proposed mechanisms for increased cholinergic tone in asthmatic patients include abnormal muscarinic receptor expression,⁴⁰ increased release of acetylcholine from cholinergic nerve endings⁴¹ and reduced levels of neuromodulators that attenuate cholinergic neurotransmission.^{42,43}

The degree to which cholinergic tone contributes to airway narrowing in asthma, either at basal state or during exacerbations, is unclear. However, the fact that airway hyper-responsiveness can

persist in asthmatic patients, possibly even in the absence of airway inflammation following long-term ICS use,⁴⁴ suggests that other pathophysiological factors, such as increased cholinergic and smooth muscle tone, have a role in asthma.^{39,45} It has been proposed that acetylcholine has a prominent role in allergen-induced airway smooth muscle remodelling.^{46–48} In a guinea pig model of ongoing allergic asthma, treatment with tiotropium inhibited increases in airway smooth muscle mass and contractility induced by allergic challenge; it has thus been hypothesised that

Box 2 Possible pathophysiological reasons why long-acting anticholinergic bronchodilators may be beneficial for the control of asthma

- Cholinergic activity is the predominant driver of bronchial smooth muscle contraction, the primary cause of reversible airway obstruction in asthma^{29–31}
- Patients with asthma have increased basal airway smooth muscle tone, possibly as a result of increased cholinergic tone^{30,35}
- Acute treatment with anticholinergic compounds reduces basal airway smooth muscle tone^{33,34}
- Local airway inflammatory mediators may have a role in inducing increased cholinergic tone^{29,31,36–39}
- Cholinergic activity may have a prominent role in airway smooth muscle remodelling^{17,46,47}
- Cholinergic receptors on lung submucosal cells regulate mucus secretion^{49,50,52}
- Increased cholinergic and smooth muscle tone may contribute to airway hyper-responsiveness^{39,44,45}
- Cholinergic antagonists may have non-neuronal anti-inflammatory actions⁵¹
- Patients with asthma may have abnormal muscarinic receptor expression⁴⁰
- Patients with asthma may have increased release of acetylcholine from cholinergic nerve endings⁴¹
- Patients with asthma may have reduced levels of neuro-modulators that attenuate cholinergic neurotransmission^{42,43}

anticholinergic drugs could help prevent airway smooth muscle remodelling in human asthma.¹⁷

Cholinergic activity is also believed to regulate non-smooth muscle and non-neuronal cells within the lungs, including inflammatory cells and those controlling mucus secretion.^{49,50} In a guinea pig model, tiotropium was shown to reduce allergen-induced mucus gland hypertrophy and goblet cell number,⁵⁰ suggesting that anticholinergic bronchodilators might also reduce airflow obstruction by reducing mucus hypersecretion. Expression of cholinergic receptors on inflammatory cells raises the additional question of whether there are any non-neuronal anti-inflammatory actions of cholinergic antagonists, although a review of studies on chronic obstructive pulmonary disease failed to identify robust evidence of this.⁵¹

PHARMACOLOGY OF ANTICHOLINERGIC BRONCHODILATORS

Anticholinergic bronchodilators are antagonistic to parasympathetic activity and exert their effects on acetylcholine receptors on airway smooth muscle and pulmonary parasympathetic nerves (Figure 2). Acetylcholine receptors fall into two families—nicotinic and muscarinic—and it is the M_1 , M_2 and M_3 subtypes of the latter that are thought to be primarily involved in the regulation of bronchoconstriction.¹⁷ All subtypes of muscarinic receptors are widely expressed in the brain, the parasympathetic nervous system and the body's smooth muscle tissues. M_1 receptors are broadly distributed throughout the parasympathetic ganglia and regulate cholinergic transmission. M_2 receptors are found in prejunctional membranes of neuromuscular junctions of airway smooth muscle and regulate negative feedback to reduce acetylcholine transmission. In a pulmonary context, M_3 receptors are predominantly expressed in smooth muscle cells, where they regulate contraction, and also within lung submucosal glands, where they regulate mucus secretion⁵² (Figure 2). Thus, it is preferable for antimuscarinic bronchodilators to have a relatively high affinity for M_1 and M_3 receptors and low affinity for the M_2 receptor.¹⁷

Currently, there are five anticholinergic drugs available for bronchodilation in respiratory disease. Ipratropium and oxitropium are short-acting non-selective antagonists of M_1 , M_2 and M_3 receptors.⁵³ In contrast, tiotropium, aclidinium bromide (aclidinium) and glycopyrronium bromide (glycopyrronium) are long-acting compounds, with comparative selectivity for the M_1/M_3 , M_2/M_3 and M_3 receptors, respectively.^{17,53,54}

Short-acting anticholinergics are generally considered less effective acute bronchodilators than SABAs, and their short duration of action makes them broadly unsuitable as controller medication. Thus, evidence of increased cholinergic tone in patients with asthma indicates that the longer-acting bronchodilator compounds may be more suitable as controller medications in asthma.

There is some rationale to suggest that the addition of long-acting anticholinergic bronchodilators to LABAs might provide advantages in the treatment of asthma (Box 2). It is reasonable to hypothesise that by simultaneously antagonising parasympathetic smooth muscle contraction and stimulating adrenergic smooth muscle relaxation, it is possible to achieve greater bronchodilation compared with either strategy in isolation. To date, there has been little thorough clinical investigation of this hypothesis in asthma, but a study in a guinea pig model found that bronchodilation induced by the LABA carmoterol was significantly augmented by the addition of tiotropium.⁵⁵ *In vitro* studies have also found that the LABA indacaterol can synergistically increase the inhibitory effects of glycopyrronium on methacholine-induced airway smooth muscle contraction.⁵⁶ As discussed below, improvements in lung function have been observed in asthmatic patients receiving tiotropium as add-on therapy to LABA plus ICS.^{26,28}

It has been suggested that anticholinergic/LABA combination therapy might offer advantages in mitigating daily variation, based on evidence that sympathetic activity may be elevated during the daytime, relative to the parasympathetic system, which may predominate at night.^{57–60} For example, it was shown in a small study in patients with nocturnal asthma that ipratropium is more effective than salbutamol in the prevention of morning reductions in peak expiratory flow.⁵⁹ It is also possible that a combined approach to bronchodilation might reduce the impact of inter-patient variability in the relative responses to anticholinergic or adrenergic interventions. Finally, tachyphylaxis to the effects of β -agonists is known to occur (although the clinical relevance of this remains unclear),^{61–63} and it has been proposed that crosstalk between muscarinic receptor signalling and adrenergic receptor signalling in smooth muscle cells might interfere with tachyphylactic mechanisms. This would provide a further rationale for the investigation of LABA/long-acting anticholinergic bronchodilator combination therapy in asthma, as add-on to ICS.⁶⁴

CLINICAL EVIDENCE OF ANTICHOLINERGIC BRONCHODILATORS IN ASTHMA

Historically, short-acting anticholinergic bronchodilators have not been considered appropriate for the control of asthma, except in some cases for the acute treatment of asthma attacks in patients with chronic stable asthma,^{17,18} and in those who experience adverse events from SABAs, such as tachycardia, arrhythmia and tremor.^{1,43} Although short-acting anticholinergics are considered less effective rapid bronchodilators than SABAs such as salbutamol,^{17,19} there are data to suggest that, for acute exacerbations, ipratropium in combination with a SABA as reliever medication improves lung function to a greater extent than a SABA alone.^{34,65,66} In a double-blind, randomised trial, Rodrigo and Rodrigo⁶⁵ investigated the effects of high-dose ipratropium plus the SABA albuterol (registered generic name for salbutamol in the USA) in adults with acute asthma, in the emergency

department. Patients receiving high-dose ipratropium plus albuterol had a greater improvement in peak expiratory flow and forced expiratory volume in 1 s compared with patients who received albuterol alone. The risk of hospital admission was 49% lower in the ipratropium/albuterol arm.⁶⁵ Further, a meta-analysis has indicated that the addition of a short-acting anticholinergic to a SABA is associated with a significant reduction in the risk of hospitalisation in children.⁶⁷ Thus, in adults or children, the main justification for the use of short-acting anticholinergic drugs in acute asthma is reduction of the elevated airway smooth muscle and cholinergic tone during an acute crisis, although administration of multiple doses has been associated with a reduction in hospitalisations and risk of hospitalisation.^{34,65–68}

Although tiotropium has been indicated for the treatment of chronic obstructive pulmonary disease for over a decade, no long-acting anticholinergic bronchodilators are currently approved in asthma. A number of compounds exist, including acclidinium, glycopyrronium, glycopyrrolate and darotroprum bromide, but, as mentioned, presently only tiotropium and umeclidinium have clinical trials in asthma listed on ClinicalTrials.gov. The latter has been under investigation in two dose-ranging Phase II trials in patients with asthma, as a monotherapy (NCT01641692) and in combination with fluticasone furoate (NCT01573624), although to our knowledge no results from these trials have yet been published.

Early studies with long-acting anticholinergics in asthma were small and underpowered, and failed to detect meaningful responses. However, studies of tiotropium and of glycopyrrolate indicated that long-acting anticholinergics can provide sustained bronchodilation and bronchoprotection.^{23,24,69,70}

To date, more thorough clinical evaluation has been performed with tiotropium only, in six Phase II or III studies, involving over 3,500 patients (Table 2). In an investigator-initiated three-way crossover trial (14 weeks per treatment) in 210 patients with asthma inadequately controlled by low-dose ICS (twice-daily beclomethasone 80 µg), tiotropium delivered via the Spiriva HandiHaler device (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA) was shown to be superior to a doubling of ICS dose and equal to the addition of salmeterol, as assessed by improvements in lung function (Table 2).²⁷

Subsequent published investigations of tiotropium have all involved administration via the Respimat SoftMist inhaler (Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany). In an 8-week crossover trial, once-daily tiotropium at a dose of 5 or 10 µg improved lung function, compared with placebo, in 107 patients with severe persistent poorly controlled asthma already receiving ICS and LABA (Table 2).²⁶ In a 16-week trial in patients with arginine/arginine homozygosity at amino acid 16 of the β_2 -adrenergic receptor (B16-Arg/Arg) and moderate poorly controlled asthma (already receiving ICS), once-daily tiotropium at a dose of 5 µg was superior to placebo and non-inferior to twice-daily salmeterol at a dose of 50 µg for maintenance of improvements in lung function (Table 2).²⁵ The rationale for performing the latter study was based on suggestions that the adverse-event profile of β_2 -agonists is worse, and the efficacy lower, in patients with the B16-Arg/Arg polymorphism,^{71,72} although prospective investigation has revealed that there are no such concerns.^{73,74} A subsequent Phase II dose-ranging study tested tiotropium at doses of 5 µg, 2.5 µg and 1.25 µg as add-on to ICS and found the 5 µg dose to provide the greatest bronchodilator effect.⁷⁵

Data from the first Phase III trial on a long-acting anticholinergic bronchodilator in asthma were published in 2012.²⁸ In two replicate trials including a total of 912 patients with poorly controlled asthma despite the use of LABA and high-dose ICS (≥ 800 µg budesonide or equivalent), tiotropium 5 µg administered via the Respimat SoftMist inhaler as add-on therapy significantly reduced the risk of severe exacerbations compared with placebo

(values provided in Table 2). Small but statistically significant improvements in lung function were also observed.²⁸ Surprisingly, given the changes in lung function and exacerbation rate, improvements in symptomatic benefit (seven-question Asthma Control Questionnaire [ACQ-7] and Asthma Quality of Life Questionnaire) were small and inconsistent. Of adverse events reported in $\geq 2\%$ of patients, only allergic rhinitis occurred at a statistically significantly higher rate in the tiotropium group compared with the placebo group. Dry mouth, a typical side effect associated with anticholinergic drugs, was reported in $\leq 2\%$ of patients.²⁸

More recently, a Phase III replicate trial of once-daily tiotropium at a dose of 5 or 2.5 µg, versus placebo, as add-on to medium-dose ICS (400–800 µg budesonide or equivalent) was conducted in 2,103 patients with poorly controlled asthma.^{76,77} An active comparator arm of salmeterol 50 µg versus placebo was also included. Again, statistically significant improvements in lung function were observed with tiotropium, which were comparable in magnitude with those seen with salmeterol. A statistically significant improvement over placebo in ACQ-7 responder rate was observed in all three active arms, although, as is common in analyses of ACQ-7 in asthma clinical trials,⁷⁸ there was also a large placebo effect.^{76,77} We await the full primary publication from this trial.

IS THERE A ROLE FOR LONG-ACTING ANTICHOLINERGIC BRONCHODILATORS IN ASTHMA?

Is it possible to determine to which patients, and in which clinical situations, long-acting anticholinergic bronchodilators might offer clinical benefits? Phase III investigation has found that tiotropium add-on therapy offers advantages to adults with severe asthma who are failing to gain control on ICS and LABA combinations.²⁸ This, and the fact that the benefit:risk ratio of ICS falls at high ICS doses,^{2,7,17,79,80} suggests that addition of long-acting anticholinergic bronchodilators to ICS plus a LABA is likely to be a useful option for patients with poorly controlled severe asthma, and an alternative to further increases in ICS dose.

Whether long-acting anticholinergics will be appropriate as alternatives to LABAs is a harder question to answer. Nevertheless, tiotropium add-on to medium-dose ICS has been shown to provide lung function and ACQ-7 improvements that were comparable with those of salmeterol,^{76,77} indicating that, in patients for whom LABAs may be unsuitable, long-acting anticholinergics could be a helpful alternative.

Although the ACQ-7 effects reported in clinical trials thus far are relatively small, it will be interesting to see to what extent in practice patients gain clinically relevant benefits in control or future risk. Further, one might expect that the demonstrated reduction of exacerbation risk with tiotropium as add-on to ICS plus LABA²⁸ might translate into long-term improvements in overall control. We anticipate that lung function improvements of the magnitude observed in the trials we have described will translate into clinically relevant benefits to patients in a real-world setting. At the time of writing, few real-world studies have been performed, as long-acting anticholinergic bronchodilators are yet to be approved in asthma. However, in a retrospective study of the UK Optimum Patient Care Research Database, off-label use of tiotropium in patients predominantly in Global Initiative for Asthma step 3 or 4 was found to be associated with a reduction in the number of exacerbations and a reduced risk of severe exacerbation or lower respiratory tract infection.⁸¹

It is yet to be determined in Phase III investigation whether long-acting anticholinergic bronchodilators offer similar benefits to adults with mild asthma or to children or adolescents, although several Phase III trials are underway with tiotropium in these populations (NCT01316380; NCT01634139; NCT01634152; NCT01277523).

Table 2. Comparison of lung function and clinical findings from clinical trials^a with long-acting anticholinergic bronchodilators in asthma

Authors	Severity ^b	Duration per treatment, weeks	N	Study drug(s)	Comparator(s)	Primary and key secondary end points	Difference from comparator ^c
Peters <i>et al.</i> ²⁷	Mild to moderate asthma inadequately controlled by low-dose ICS	14	210	Once-daily tiotropium 18 µg, via Spiriva HandiHaler	Doubling ICS dose	Morning PEF	25.8 l/min (95% CI: 14.4–37.1; $P < 0.001$)
					Doubling ICS dose	Daily symptom score	–0.11 points ($P < 0.001$)
					Salmeterol	Morning PEF	No significant difference
					Salmeterol	Daily symptom score	No significant difference
Kerstjens <i>et al.</i> ²⁶	Severe asthma inadequately controlled by high-dose ICS + LABA	8	107	Once-daily tiotropium 5 µg, via Respimat SoftMist	Placebo	Tiotropium 5 µg, peak FEV ₁	139 ml (95% CI: 96–181; $P < 0.0001$)
						Asthma-related health status or symptoms	No significant difference
				Once-daily tiotropium 10 µg, via Respimat SoftMist		Tiotropium 10 µg, peak FEV ₁	170 ml (95% CI: 128–213; $P < 0.001$)
						Asthma-related health status or symptoms	No significant difference
Bateman <i>et al.</i> ²⁵	Mild to moderate asthma uncontrolled by ICS alone	16	38	Once-daily tiotropium 5 µg, via Respimat SoftMist	Placebo (following run-in with salmeterol) ^d	Morning pre-dose PEF	–20.70 l/min (95% CI: –33.24 to –8.16; $P = 0.001$ for superiority)
					Salmeterol (following run-in with salmeterol)	Morning pre-dose PEF	–0.78 l/min (95% CI: –13.096 to 11.530; $P = 0.002$ for non-inferiority)
Kerstjens <i>et al.</i> ²⁸	Poorly controlled asthma despite use of ICS + LABA	48	912	Once-daily tiotropium 5 µg, via Respimat SoftMist	Placebo	Peak FEV ₁ at week 24	86 ± 34 ml ($P = 0.01$) (trial 1); 154 ± 32 ml ($P < 0.001$) (trial 2)
						Trough FEV ₁ at week 24	88 ± 31 ml ($P = 0.01$) (trial 1); 111 ± 30 ml ($P = 0.001$) (trial 2)
						Reduction in risk of severe exacerbation at week 48	21% (hazard ratio 0.79; $P < 0.03$) (pooled population)
						Difference in AQLQ	0.04 units, NS (trial 1) ^e 0.18 units, $P = 0.02$ (trial 2) ^e
						Difference in ACQ-7	–0.13, NS (trial 1) ^e –0.2, $P = 0.003$ (trial 2) ^e

Abbreviations: ACQ-7, seven-question Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; NS, not significant; PEF, peak expiratory flow.

^aOnly studies published in journal primary publication format have been included (Kerstjens *et al.*^{76,77} and Beeh *et al.*⁷⁵ not shown).

^bAll studies were in adults.

^cAll lung function values are mean change from baseline, unless otherwise stated.

^dActive treatments were evaluated as maintenance therapies following a 4-week run-in period with salmeterol.

^eMinimal clinically important difference not achieved.

There are some physiological (Box 2) and clinical rationales that allow us to suggest groups of patients for whom long-acting anticholinergic bronchodilators might be appropriate. A few small studies with short-acting anticholinergic bronchodilators have indicated that responses to anticholinergics are more likely in older patients^{82,83} or in those with intrinsic (non-allergic) asthma.⁸⁴ It has also been suggested that patients intolerant of β_2 -adrenergic agents or with nocturnal asthma might respond better to anticholinergic bronchodilators.¹⁷ Further, there is evidence that

patients with non-eosinophilic sputum profiles^{85,86} or neutrophilic inflammation do not gain the same benefit from ICS as those with eosinophilic inflammation,⁸⁷ and hence may be candidates for additional treatments such as long-acting anticholinergic bronchodilators, as may groups in which steroid resistance is known to occur, such as smokers or obese patients.^{88,89}

It is currently unclear why long-acting anticholinergic bronchodilators might reduce the rate of exacerbations. However, one can hypothesise that a contributing factor to

exacerbations might be an increase in afferent sensory nerve activity, resulting in an increase in parasympathetic tone and subsequent bronchoconstriction. If this were the case, treatment with long-acting anticholinergic therapies may attenuate such autonomic effects and provide additional bronchodilation.

CONCLUSIONS

It has long been apparent from clinical and preclinical investigations of the pathophysiology of asthma that cholinergic parasympathetic tone contributes to contraction of bronchial smooth muscle and narrowing of the airways. The extent to which increased parasympathetic tone is a consequence of reflex to the inflammatory state or is a pathophysiological mechanism in itself is unclear. Regardless, the raised parasympathetic tone does provide a rationale for the use of long-acting anticholinergic bronchodilators in asthma, and recent Phase III trial results have demonstrated clinical benefits and lung function improvements with tiotropium as add-on therapy to ICS alone or ICS plus LABA in adult patients with poorly controlled asthma. In light of the evidence, we believe that anticholinergic bronchodilators will be a useful add-on therapy for patients at high risk of future worsening or exacerbations, and in patients whose asthma remains uncontrolled on a broad range of treatments and/or for whom other alternative therapies are unsuitable.

Whether tiotropium or other long-acting anticholinergic bronchodilators will offer clinical advantages in younger patients, or in those with less severe asthma than studied thus far, is under investigation. As we gain clinical experience in asthma with long-acting anticholinergics, if approved, it will be interesting to see whether and to what extent certain subgroups and phenotypes benefit from their use as controller medications.

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The authors take full responsibility for the scope, direction, content of, and editorial decisions relating to, the manuscript; they were involved at all stages of development and have approved the submitted manuscript. DP provided the initial scope, flow, topics and search term areas to be included in the manuscript outline. DP, LF, AK, TvDM and MRR all provided input and guidance on content, style, flow, figures and reference sources on all subsequent drafts of the outline and the full manuscript. All authors provided their approval of the final draft of the manuscript. Medical writing assistance, in the form of literature searches and preparation and revision of the draft manuscript, was provided by Sam Yarwood, PhD, of Complete HealthVizion, under the authors' conceptual direction and based on feedback from all authors.

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